DIAGNOSIS, TREATMENT, AND MANAGEMENT OF PRIMARY OPEN-ANGLE GLAUCOMA

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Primary Open-Angle Glaucoma is perhaps one of the most challenging diseases faced by today's eye care professional. This is greatly attributed to the fact that its complexity requires the doctor to consider numerous factors in not only diagnosing POAG, but also in treating and managing the disease. This paper will attempt to decipher and summarize each of these areas with special emphasis on treatment and management. Though treatment with surgical procedures is quite prevalent today, it will only be considered as a viable referral option.

Three major diagnostic signs used in evaluating for POAG are increased intraocular pressure, optic disc changes, and visual field defects. IOP is a significant diagnostic tool but rather enigmatic in application. To explain, intraocular pressures between 11 mm Hg and 21 mm Hg are traditionally considered to be normal. Studies have shown that 97.5% of the population has an IOP less than 21 mm Hg and 97.9% of the population has an IOP less than 24 mm Hg. Also, there is general consensus that if a patient has an untreated IOP greater than 30 mm Hg he/she is likely to develop glaucoma. However, a patient could have a pressure over 21 mm Hg and have no signs of glaucoma. This group of patients is called ocular hypertensive.

Surveys indicate that between 2% and 12% of the population over 40 yrs. old are ocular hypertensive. However, over a 5 to 15 yr. period, only 0.5% to 1.0% per year of these ocular hypertensive patients will develop glaucoma. Thus, since not all ocular hypertensive patients develop glaucoma, a doctor cannot simply treat everyone with high intraocular pressures. The doctor must consider that glaucoma medication is expensive, there are various side effects, and the treatment is generally lifelong.

There are three general scenarios in which most doctors would start treatment in an ocular hypertensive patient. The first is a patient who has greater than 30 mm Hg. The second is a patient with between 21 mm Hg and 30 mm Hg and has two or three risk factors for glaucoma such as family history, diabetes, or hypertension. A third situation is when the IOP is between 25 mm Hg and 30 mm Hg and the patient responds well to a trial of topical medication without any side effects.

On the other end of the spectrum, a patient could have an IOP pressure under 21 mm Hg and have signs of glaucoma. This type of glaucoma is called normal tension glaucoma. This demonstrates that an IOP that is acceptable for one patient may cause ocular damage for another. It has been noted that the risk for ocular damage increases as the IOP increases. Armaly found that while 0.8% of patients with an IOP of 16 mm Hg or less developed glaucomatous damage, 8.4% of patients with an IOP of 24 mm Hg or higher developed glaucomatous damage. Thus, it is apparent that IOP must be used with many other factors when diagnosing someone with glaucoma.

Two such factors that can assist in the diagnosis are abnormal diurnal variation and asymmetry of IOP between the eyes. Abnormal diurnal variation is a risk factor for glaucoma. The average diurnal IOP variation is 6.4 mm Hg in normal patients, 8.4 mm Hg in ocular hypertensive patients, and 13.3 mm Hg in patients with glaucoma. Two cases clearly illustrate the importance of diurnal variation in the diagnosis and management of glaucoma. In one case, a 55 yr. old patient was being followed for a number of years for suspicious optic nerve cupping. His cups were getting progressively larger, but his

pressures were tested each morning and found to be continually around 21 mm Hg. They finally decided to have him come in an afternoon and it was then determined that his pressures were actually close to 30 mm Hg in both eyes. In another case, a woman had been receiving glaucoma treatment for several years. She was generally seen in the morning when her pressures were around 16 mm Hg. Her treatment was based solely on these readings and considered adequate. However, she was on one occasion seen late in the evening and her pressures were actually found to be in the low 30's. These scenarios stress the importance of not only noting the time of the day each pressure is taken, but also the significance of taking pressures at various times throughout the day. If the pressure is taken only at one time during the day, the doctor may miss when the patient's diurnal variation is at its highest point. This is not only important for the diagnosis, but also for the treatment and management of a patient with glaucoma. As a side note, it has been estimated that a single tonometric screening may miss between 30% and 50% of glaucoma patients. Most agree that any diurnal pressure variation over 6mm Hg should be considered suspicious and further investigated.

Asymmetry of between the eyes can also be a significant risk factor. Studies have shown that only five percent of the normal population has an IOP difference of 5 mm Hg and 17% have a difference of 3 to 4 mm Hg. The doctor should closely examine any patient with asymmetries greater than 5mm Hg.

Evaluation of the optic disc is an even greater diagnostic tool than IOP. There are several characteristics of the optic disc that a doctor may examine in the investigation process for glaucoma. One

such example is the C/D ratio. Yablonski et al performed a comparison study of normal and glaucomatous eyes and determined that C/D ratios greater than 0.4 must be examined very carefully. Any ratios .6 or higher are considered to be of high risk for glaucoma.

It must be noted that a patient may have a large cup and be quite healthy. However, the risk intensifies when the C/D ratio tends to progressively increase in a given patient. Detection of this increase can be a rather arduous task. In fact, Odberg and Riise assert that intraobserver variations in the assessment of the C/D ratio can be far too great to be effectively utilized in the early detection of glaucoma. Thus, they recommend that stereo disc photographs be taken especially in the long- term follow-up of ocular hypertensive patients.

Two primary methods of measuring optic cup size are pallor/color and cupping/contour. Pallor is the area of maximum color contrast. Contour of the optic disc is any depression below the retinal surface. A C/D ratio determined by contour which is greater than a C/D ratio determined by color will increase the risk of glaucoma. It must also be considered that there are different ways in which the cup may enlarge. Focal enlargement of the cup which is referred to as polar notching usually occurs at the superior and inferior poles of the disc and creates a larger C/D ratio vertically. This enlargement typically moves toward the rim where it becomes weakened and creates apparent breaks in the vessels crossing at that point, often called bayonneting of the vessel. The cups may also enlarge in concentric circles. The circles may unfold in any direction, but the nasal rim is generally resistant to change.

Peripapillary crescents or halos in the disc have also been found among glaucomatous patients. It appears that as erosion of the neural retinal rim approaches the edge of the disc, peripapillary atrophy is more likely. However, halos and crescents also occur in other conditions and can be entirely normal.

Another feature of the disc that may indicate glaucoma are small linear hemorrhages that are on or near the disc. Several studies have shown that linear hemorrhages increase the probability of visual field loss developing among patients with ocular hypertension. Studies have also demonstrated that linear disc hemorrhages are more prevalent among patients with POAG than in those with simply elevated IOP and no visual field loss. Thus, linear hemorrhages may be useful both as a diagnostic tool and as an indicator to the doctor that there is poor control of the glaucoma. It must also be noted that splinter hemorrhages occur in other optic nerve head conditions such as ischemic optic neuropathies, blood dyscrasias, and posterior vitreous detachments.

Similar to IOP's, asymmetry of the C/D ratio between the eyes is also a significant detection sign of glaucoma. Though glaucoma is a bilateral disease, it is generally more advanced in one of the eyes. Armaly has shown that 99% of normals have an asymmetry of 0.2 or less and that 53% of the glaucomatous population have an asymmetry greater than 0.2. This sets the precedence that patients with asymmetries of 0.2 or greater between the eyes should be examined closely for the possibility of glaucoma.

Another feature of the disc that should also be evaluated for glaucoma is decentration of the cup or notching of the neuroretinal rim.

The optic cup is usually located in the center of the disc. A displacement of the cup as well as a notch in the rim can be early indications for glaucoma. Also when inspecting the neuroretinal rim, the doctor should note whether the rim has a uniform thickness all through 360 degrees of the optic nerve. If the rim becomes thin in some places, the rim may be atrophying.

Visual fields is not only an important aspect of diagnosing glaucoma, but it is also utilized in the control and management of the disease. The Humphrey Field Analyzer is one of the most commonly used instruments to measure visual fields. Just as with IOP and optic disc changes, interpreting visual fields can also be rather arduous due to the numerous variables that may affect the measured threshold.

Though visual field defects can vary considerably, there are certain classical features unique only to glaucoma. In the central 20 degrees of the field, small paracentral scotomata occur as the earliest glaucomatous defects in 70% to 80% of the cases. These defects occur most often superiorly. A nasal step visual field defect occurs in approximately 6% to 18% of the cases. Temporal constriction which can occur above or below the horizontal in the temporal field is usually sectoral-shaped, but can assume other forms. Studies have shown that between 3% to 6% of glaucoma patients have temporal constriction.

Not all glaucomatous patients will necessarily present each of the described visual field defect patterns. One of the more recent concepts is that glaucoma may cause a diffuse visual field loss, meaning that there is a decrease in threshold values across the visual field or a depression in the hill of vision.

Another factor that deserves careful consideration in utilizing visual field analysis for glaucoma are peripheral fields. The mainstay of automated glaucoma testing has been the central 30 degree programs. However, in 10% to 15% of glaucoma cases visual defects were found not in the central 30 degrees, but rather in the peripheral nasal field. Early defects can also occur in the temporal region of the visual field. Though it may require additional time to test in both the central and peripheral regions, the potential rewards of early glaucoma detection are certainly significant.

The doctor must also consider that there are several factors which can affect the measured threshold. For example, some studies indicate that some people may demonstrate a learning effect when taking visual fields. Patient reliability is also a significant concern in interpreting visual fields. It should be noted that a high number of false negative errors may not necessarily mean that the patient is unreliable, rather that he/she may have a diseased retina. Proper correction of the refractive is also important. A refractive error of only one diopter can cause a significant decrease of the measured threshold. Aphakic patients should be tested with contact lenses since aphakic spectacle corrections induce peripheral artifacts. Also, the pupil size should be at least 3mm or greater and recorded each time the test is performed. If the patient was first tested with dilation, then all subsequent tests must be with dilations. Finally, diagnosis of glaucoma or a change in the treatment plan must not be based on one visual field test, rather a second test should be performed to substantiate the visual field deficit.

One of the most notable challenges in visual field testing is the differentiation of long-term fluctuation (test-retest variation) from true progression of visual field loss. Many studies have shown that test-retest variations in computerized perimetry is considerable among individuals and this variation is especially large in glaucomatous visual fields. In addition, deeper visual field defects will show more random variation in threshold than a shallow defect or a normal point. Thus, it can make it rather difficult to differentiate normal variation from true progression of visual field loss.

In summary, interpreting IOP, optic disc changes, and visual field loss in evaluating for POAG is certainly not an easy task. Unfortunately, there is no documented "formula" that delineates how POAG can be diagnosed. The doctor must consider the past data and indications described above as well as resort to personal experience.

Once diagnosed, the doctor primarily has available four major groups of treatment medications. These include the beta-adrenergic antagonists, adrenergic agonists, cholinergic agonists, and carbonic anhydrase inhibitors. Though there are certainly a variety of drugs the doctor must choose from, analyzing their advantages and disadvantages can help to narrow the selection process.

Beta-adrenergic antagonists known as beta-blockers are the most commonly prescribed medications for the treatment of glaucoma. They are often considered as the first drugs of choice, unless the patient shows contraindications. Studies have shown that blacks respond better to beta blockers than the other drugs. It has been noted that beta blockers reduce aqueous humor formation. In addition, while some

patients may be discontinued due to side effects, they are generally well tolerated by most patients.

One of the most common ocular side effects is burning or stinging with installation. Other ocular side effects are corneal anesthesia, corneal erosion in contact lens wearers, allergic conjunctivitis, ptosis, and visual or refractive disturbances. The central nervous system is the site of the most frequent systemic side effects. Some of these more common side effects include lethargy, lightheadedness, weakness, fatigue, mental depression, and memory loss. The onset of these symptoms can vary from a few days to several months following therapy initiation. For most patients, these symptoms tend to be mild and temporary. However, it may require discontinuation for those with more severe reactions.

The second most common type of side effects involve the cardiovascular system. These include bradycardia, systemic hypotension, arrhythmia, syncope, and heart blockage. It has been reported that beta blockers can also alter symptoms of hypoglycemia. They may increase hypoglycemic episodes, thus altering the response to glucose administration. Thus, extreme caution must especially be used when treating diabetic patients.

Beta blockers have also been noted to cause certain types of respiratory complications. Wheezing and shortness of breath are the most common. Others reactions such as pulmonary failure, asthma, and bronchitis have especially been reported among patients with previous chronic obstructive pulmonary disease.

Beta blockers can also cause certain interactions when used with other systemic medications. Caution must be utilized if the patient is

concurrently taking the following medications: Calcium channel blockers, sympathomimetics, digitalis, reserpine, and systemic beta antagonists. In most cases, patients can safely use topical beta blockers while also taking systemic beta blockers. The systemic beta blockers are additive in the ocular hypotensive effect with the topical beta blockers.

Some of the major beta blockers available today are timolol, levobunolol, betaxolol, and metipranolol. Timolol is the most commonly prescribed beta blocker. It is also the most commonly prescribed glaucoma medication. It is a nonselective beta-1 and beta-2 antagonist. It is available in 0.25% and 0.50% concentrations in solution form and is recommended to be used twice daily at 12 hour intervals. The reduction of IOP usually begins within one hour after administration and reaches a maximum effect after two hours. The response from timolol can be as high as a 40% reduction in baseline IOP over the first few weeks. This effect will generally decrease over the first six months to approximately 23% to 33% reduction in IOP; a phenomenon is called "short- term escape." In addition, it has been noted that timolol decreases in effectiveness after being used for more than one year. This phenomenon has been termed "long- term drift." There is controversy over whether timolol is additive with epinephrine or dipivefrin in its hypotensive effect. If there is any additive effect, it is usually rather small and ranges from 2 to 3 mm Hg.

Some of the side effects noted specifically with timolol are dry eye and superficial punctate keratitis following long-term treatment. There is often some burning on instillation, but usually subsides within the

first week of therapy. One of the most frequent reasons for discontinuation of timolol therapy is blurred vision.

Levobunolol is another major beta blocker. It is similar to timolol in many regards. It is a non-selective beta-1 and beta-2 antagonist and available in 0.25% and 0.50% solutions. What differentiates levobunolol from timolol and other beta blockers is it has a longer duration of action and may be used once a day. Because of individual variations, levobunolol is often used twice daily. The reduction of IOP is approximately 23% (7.0 to 9.4 mm Hg).

Betaxolol is a selective beta-1 antagonist and is available as 0.5% solution and as a 0.25% suspension. Hypotensive effects range from approximately 11% to 29% based on twice daily administration at 12 hour intervals. Studies have shown that betaxolol is not as effective in its ocular hypotensive effects as timolol or levobunolol. But, it has shown to have better additive effects with epinephrine and dipivefrin as compared to other beta blockers. Because betaxolol is beta-1 selective, it is less likely than non-selective beta blockers to cause respiratory complications. However, since its beta-1 selectivity is not absolute it still has the potential to cause respiratory problems in high risk patients. Betaxolol is, nonetheless, the preferred drug of choice for Chronic Obstructive Pulmonary Disease patients who require a beta blocker for glaucoma treatment.

Some reports indicate that betaxolol may be less likely to induce central nervous system and cardiovascular complications as compared to other beta blockers. Some of the ocular side effects of betaxolol are mild to moderate burning or stinging upon instillation. The 0.25%

suspension form minimizes stinging and adds to patient comfort without compromising the hypotensive effect.

Metipranolol is a non-selective beta blocking agent which is similar to timolol and levobunolol in its action. It is available as a 0.3% solution with twice daily administration at 12 hour intervals. The only distinguishing characteristic of metipranolol in comparison to other beta blockers is its lower cost.

Adrenergic agonists comprise the second major group of glaucoma medications. Epinephrine and dipivefrin are the significant drugs in this group. One of the most significant ocular side effects of adrenergic agonists is the formation of cystoid macular edema which occurs in more than 20% of aphakic eyes. Other common ocular side effects include hyperemia, burning, irritation, tearing, allergy, and blepharoconjunctivitis.

Systemic side effects are less common than ocular side effects with the use of adrenergic agonists. These include systemic hypertension, premature ventricular contractions, tachycardia, palpitations, anxiety, headache, and browache. Risk of systemic side effects increases when adrenergic agonists are used in conjunction with certain systemic medications such as monoamine oxidase inhibitors, antihistamines, and tricyclic antidepressants.

Adrenergic agonists are additive in their ocular hypotensive effect with miotic cholinergic agonists, oral carbonic anhydrase inhibitors, and to a smaller degree with beta blockers as stated earlier. There is also more of a likelihood of pupil dilation occurring when beta blockers are used at the same times as adrenergic agonists; thus, they should be avoided in narrow angle patients.

Epinephrine is an alpha and beta direct acting sympathomimetic. It increases outflow facility and decreases production of aqueous. It is available in three forms: hydrochloride, bitartate, and borate. The solutions are available in concentrations of 0.5%, 1%, and 2%. There is usually a reduction in IOP one hour after administration; reaching a maximum effect in 2 to 6 hours, and returning to baseline in 12 to 24 hours. Epinephrine should be given twice daily 12 hours apart. The reduction in IOP ranges from 15 to 21 percent.

Epinephrine can occasionally be associated with notable and prolonged rise of intraocular pressure in patients with POAG. The mechanism is unknown but caution should be exercised with uniocular patients and those patients with advanced glaucoma. This phenomenon appears to be less notable when miotics are currently being used. Epinephrine can also cause formation of adrenochrome pigment deposits of the conjunctiva and occasionally in the corneal epithelium. Epinephrine has also been reported to stain hydrogel contact lenses.

Unlike epinephrine, dipivefrin will not stain hydrogel lenses. Dipivefrin is actually a prodrug of epinephrine. It is lipophilic and better absorbed into the eye; thus, can be used in lower concentrations than epinephrine. A 0.1% solution of dipivefrin is approximately equal to 1% or 2% of topical epinephrine. The recommended administration is twice daily. The reduction of IOP ranges from 15% to 26%. Because dipivefrin is used in lower concentrations, the ocular and systemic side effects are much less severe. Its corneal penetration is 17 times that of epinephrine. It is generally available only in a 0.1% solution. Intraocular pressure reduction occurs within one hour after

administration and reaches its maximum effect by 4 to 8 hours. Baseline IOP is reached after 12 to 24 hours.

The third major group of glaucoma medications are the cholinergic agonists. They increase aqueous outflow facility. Pilocarpine, carbachol, and echothiophate are the most commonly used drugs in this category. Of the three, pilocarpine by far is the most commonly used cholinergic agonist. Pilocarpine and carbachol are both direct acting cholinergics and act in the same manner as the neurotransmitter acetylcholine by stimulating parasympathetic receptors. Echothiophate is an indirect-acting cholinergic agonist and works by inhibiting the action of the enzyme cholinesterase and therefore increases the effect of acetylcholine.

Ocular side effects are relatively common with cholinergic agonists, and for a substantial number of patients it must be discontinued due to complications. One of the most disconcerting ocular side effects is accommodative spasm which can last up to 2 to 3 hours following the instillation of the topical solution. This is only a problem for those individuals under the age of 40 who have active accommodative systems. Some ways to prevent spasms include using lower concentrations, applying the gel or ocusert form of pilocarpine, or by using a clip-on minus prescription during the period of blurred vision.

Another side effect of the cholinergic agonists is miosis. This can cause a reduction in vision in dim illumination and in those patients with nuclear sclerotic or posterior subcapsular cataracts. The problem can be overcome by the concurrent use of phenlyephrine. This will not affect the IOP and may permit sufficient improvement in visual acuity to allow the patient to continue using cholinergic agonists.

There is an association between cholinergic agonists and retinal detachment. Patients with peripheral retinal diseases or myopia may be at a greater risk of developing retinal detachment when placed on miotic therapy. Thus, caution should be exercised with these types of patients.

Posterior synechiae formation is common after long-term use of cholinergic agonists. However, periodic pupil dilation which is necessary for follow-up treatment in patients with glaucoma will reduce the risk of the pupil becoming bound down from posterior synechiae. Other ocular side effects of cholinergic agonists include follicular conjunctivitis, ciliary and conjunctival congestion, lid myokymia, frontal headache, and ocular or periorbital pain.

The systemic side effects that are found with the direct acting cholinergic agonists such as pilocarpine and carbachol are rare. The adverse reactions are occasionally found in those patients who are receiving frequent instillations of the drug for the treatment of acute angle-closure glaucoma. Some of the systemic side effects that can occur from the use of these drugs include salivation, bradycardia, systemic hypotension, perspiration, nausea, vomiting, diarrhea, bronchospasm, pulmonary edema, and abdominal pain. The risk of systemic side effects of indirect acting cholinergics can be increased for farmers who come in contact with organosphosphate pesticides and fertilizers. Also, the action of succinylcholine used for general anesthesia may be prolonged leading to prolonged respiratory paralysis for those patients using indirect acting cholinergics.

Pilocarpine as stated earlier is by far the most commonly used cholinergic agonist for the treatment of POAG. It is available as a

solution ranging from 0.25% to 10%, a solution combined with epinephrine bitartate ranging from 1% to 6% concentration, an insert delivering either 20 ug/h or 40 ug/h, and a 4% gel. The most commonly prescribed solutions are the 1,2, and 4 percent. Reduction of IOP begins one hour after administration and lasts from 4 to 8 hours. The most commonly prescribed administration is 4 times daily at 6 hour intervals. Alternate delivery systems were designed to try to improve compliance and to reduce the number of side effects which can be a problem when administered 4 times daily. The pilocarpine ocusert is placed in the inferior cul-de-sac and provides sustained release of pilocarpine up to a week. The 20 ug/h has a therapeutic effect similar to the 1% and 2% pilocarpine solution administered 4 times daily. The 40 ug/h has a therapeutic effect similar to the 2% to 4% pilocarpine solution administered 4 times daily. Some of the advantages of the ocusert form include reduced miosis and accommodative spasm for younger individuals and better diurnal control than with the 4 times daily administration. However, there are some noted complications with the ocusert form including difficulty with insertion, dislodging from the cul-de-sac, and patient discomfort.

Pilocarpine is also available in another gel form, called Pilopine HS gel. The 4% gel which is administered at bedtime is equal in its therapeutic effect to the 2% pilocarpine solution administered 4 times per day. There is some question as to whether the gel provides adequate control of the IOP over the 24 hour period. Some doctors feel the gel loses its effectiveness 14 to 18 hours after its administration. It is advised to check the IOP of the patient at this time and if necessary have the patient add a single drop of the 2% solution.

There are a few additional side effects unique to pilocarpine as a cholinergic agonist. This drug has been shown to hasten the development of cataracts with long- term use. Allergic conjunctivitis and dermatitis occasionally occur after long- term use of pilocarpine solutions, particularly if it contains the preservative benzalkonium chloride. The problem is usually corrected by changing the solution to a different preservative.

Carbachol is the other direct acting cholinergic agonist used in the treatment of POAG. It is available in 0.75%, 1.5%, 2.25%, and 3% solutions. Carbachol is more potent than pilocarpine for an equivalent concentration and has a longer duration of action than pilocarpine. Due to its longer duration of action, it can only be used 2 to 3 times per day.

Echothiophate is a very potent cholinergic agonist which is usually reserved for the advanced stages of POAG. It is available in solutions ranging from 0.03% to 0.25%. The most commonly prescribed solutions are the 0.03% and the 0.06%. The 0.03% solution has a therapeutic effect similar to pilocarpine 2% solution. The 0.06% has a therapeutic effect similar to the 4% solution. There exist greater risks of ocular and systemic side effects with the use of echothiophate in comparison to the other cholinergic agonists. Echothiophate specifically increases the risk of retinal detachment, cataract formation, and respiratory distress.

The fourth major group of medications are the carbonic anhydrase inhibitors(CAI's). They decrease IOP by reducing aqueous formation. These drugs are not used topically, rather only in systemic administration forms. There are a significant number of side effects

caused by the CAI's; thus, limiting their usefulness. Studies have shown that less than 50% of patients can be maintained on long-term therapy with these type of drugs. They are very potent hypotensive agents and can reduce IOP by up to 40%. The major carbonic anhydrase inhibitors available today are acetazolamide, methazolamide; and to a lesser degree, dichlorphenamide.

Ocular side effects associated with CAI's are extremely rare. Some of the most common systemic side effects are numbness and tingling of the fingers, toes, and perioral region. Other non-ocular side effects which are common are abdominal cramps, nausea, and diarrhea. If less than the maximal CAI doses are used, these symptoms are usually tolerable and often transient. Some of the side effects that are most likely to result in discontinuation of the CAI'S are malaise, fatigue, weight loss, depression, anorexia, and decreased libido.

Many of the side effects that occur with the use of CAI's are due to the resultant systemic acidosis. Certain systemic diseases and the use of some systemic medications can cause some patients to be particularly susceptible to the side effects of the carbonic anhydrase inhibitors. Some of these systemic diseases are Chronic Obstructive Pulmonary Disease, liver cirrhosis and sickle cell hemoglobinopathies. Some of the medications that can increase the risk of side effects with CAI's are potassium-depleting diuretics and patients taking digitalis preparations.

Acetazolamide is one of the most commonly used carbonic anhydrase inhibitors. It is available in tablet form in 125 mg and 250 mg preparations and in a time release 500 mg capsule form. It is also available as an intravenous preparation in a 500 mg vial. The

administration schedule for the 125 mg and 250 mg tablets is four times daily and for the 500 mg capsule is twice daily. However, it is advised to first begin with a reduced administration schedule of twice daily for the 125 mg and 250 mg tablets and once daily for the capsule to minimize its potential side effects. If further reduction of IOP is needed, then more frequent doses may be administered. IOP begins to decrease within 60 minutes after administration and reaches a maximum effect within 2 to 4 hours after administration. The time-release capsule begins to decrease IOP 2 hours after administration and reaches its maximum effect within 8 hours. Its duration of action ranges from 12 to 24 hours.

Acetazolamide alters kidney metabolism. It can cause alkaline urine which then has the potential to create renal calculi and metabolic acidosis. This drug also increases urinary excretion of potassium. However, problems associated with hypokalemia are rare. Acetazolamide is also associated with blood dyscrasias, which are very serious side effects. Though these are very rare, they include thrombocytopenia, agranulocytosis, and aplastic anemia.

Methazolamide in recent years has become the first choice CAI over acetazolamide because of its lower chance of causing renal disease or complications in patients with cardiopulmonary problems. This drug is especially useful for patients who are predisposed to develop renal calculi. The use of methazolamide has rarely been associated with kidney stones. Patients who are not able to tolerate acetazolamide may be able to tolerate methazolamide.

Other side effects of methazolamide are similar to acetazolamide. However, methazolamide does have greater diffusion capabilities into

both the eye and the central nervous system than acetazolamide. Subsequently, CNS side effects are somewhat greater for methazolamide than for acetazolamide.

Methazolamide is available in 25 mg and 50 mg tablets. Administration for methazolamide is 2 to 3 times daily. The reduction of IOP begins 1 to 2 hours after administration and reaches a maximum effect within 6 hours after administration. The duration of action ranges from 12 to 14 hours.

Dichlorphenamide has side effects similar to that of acetazolamide. However, the side effects of dichlorphenamide occur more frequently and are more severe than those with acetazolamide. Patients have more trouble tolerating dichlorphenamide than the other carbonic anhydrase inhibitors. This drug is available in 50 mg tablets. The reduction of IOP begins 30 minutes after administration and has a duration of action of 6 to 12 hours.

In summary, though the number of available glaucoma drugs are numerous, the appropriate treatment regimen is very patient specific. There are many important factors that the doctor needs to consider such as the patient's age, current systemic and ocular health conditions, and any medications that the patient is currently receiving before selecting the appropriate drug.

Understanding the application and efficacy of the various POAG drugs can be facilitated by highlighting some of the clinical studies. As stated previously, beta blockers are the first drugs of choice in most cases of POAG unless there are contraindications to their use. Two primary concerns with the use of beta blockers are systemic side effects and compliance. The maximum recommended dosage for timolol

or levobunolol is traditionally 0.5% administered twice daily. A study was performed by Silverstone et al which evaluated the hypotensive efficacy at lower levels of 0.25% levobunolol and 0.25% timolol administered once daily. This study was conducted over a 3 month period with 80 patients who either had open-angle glaucoma or ocular hypertension. Their pressures ranged from 22 to 32 mm hg. These patients were broken down into 2 groups. One group of 39 patients were given 0.25% levobunolol administered once daily; the other group of 41 patients were treated with 0.25% timolol administered once daily. Patients were instructed to instill their medications between the hours of 7:00 a.m. and 9:00 a.m. Follow-up visits were scheduled in the morning and were taken before the patients had instilled their medications. Thirty-seven of the thirty-nine patients in the 0.25% levobunolol group and 35 of the 41 patients in the 0.25% timolol group successfully completed the study. In the 3 month study, the overall mean decreases in intraocular pressure were 5.3 mm Hg in the 0.25% levobunolol group and 5.4 mm Hg in the 0.25% timolol group. Side effects on mean heart and blood pressure were minimal. As a result, this study demonstrates that the lower levels of 0.25% levobunolol and 0.25% timolol are equally effective therapy in controlling mild to moderately elevated intraocular pressures.

Other supporting studies have demonstrated that 0.5% timolol and 0.5% levobunolol are also effective in controlling intraocular pressure on a once daily administration. Another study reported that levobunolol administered twice daily was equally effective as 0.5% levobunolol administered once daily in mean intraocular pressure reduction. It can be summarized that levobunolol and timolol can both be used in lower

concentrations and less frequency administrations than the recommended levels. This can be valuable in enhancing patient compliance as well as systemic safety.

Timolol is the most frequently prescribed beta blocker for the treatment of POAG. One of the concerns that has been found with timolol is long-term drift, a loss of effectiveness after long periods of use. A six month study was conducted by Gandolfi to see if taking a short break from timolol use would restore the patient's sensitivity to the drug. The patients in the study had been using timolol eye drops twice daily from one to four years before developing a drift. The patients were divided into two groups. In one group, timolol was withdrawn and replaced with 0.1% dipivefrin eye drops administered twice daily for either 30 or 60 day duration. The second group of patients had timolol withdrawn and replaced with artificial tears for either 30 or 60 day duration. Timolol was re-initiated to both groups after their 30 or 60 day periods. The intraocular pressure was checked the day before restoring timolol as well as 7, 60, 120, and 180 days after restoring timolol.

When considering the group of eyes in which timolol was withdrawn and replaced by artificial tears, there was a low but significant recovery of sensitivity to timolol. The mean decrease in IOP was 3.5 mm Hg plus or minus 1.2 mm Hg for the 30 day period and 3.7 mm Hg plus or minus 1.6 mm Hg for the 60 day period. However, after 2 months, the restoration of sensitivity to timolol was no longer maintained and the IOP returned to the pre-withdrawal value.

A different situation occurred in the eyes treated with dipivefrin both for the 30 and 60 day periods. The mean IOP decrease for the 30

day treatment of dipivefrin was 7.7 mm Hg plus or minus 1.2 mm Hg. The mean IOP decrease for the 60 day treatment of dipivefrin was 8.5 mm Hg plus or minus 1.5 mm Hg. However, in the 30 day treatment, the IOP remained unchanged for 2 months; then returned to the pre-withdrawal value after 4 months. In contrast, the 60 day group maintained a low IOP in all subsequent follow-up visits, resulting in a prolonged restoration of sensitivity to timolol. Unfortunately, because the study lasted for only six months, it was unknown when and if reoccurrence of the long-term drift took place.

Numerous past studies have supported that a high number of daily doses of any medication tends to lower patient compliance which effects drug efficacy. Timolol and pilocarpine are frequently prescribed together when patients are inadequately controlled by timolol alone. Timolol is usually administered twice daily, while pilocarpine is administered three or four times daily. A study was conducted by Loefors and Viksmoen to test the efficacy of a new single-drop combination of timolol and pilocarpine in two different concentrations administered twice daily. There were sixteen patients in the study that were divided into three groups and treated for 49 days. All three groups were initially administered timolol 0.5% twice daily for 20 days. Then, one group received timolol 0.5% twice daily for another 29 days. The second group was administered one drop of the combination timolol 0.5% and pilocarpine 2% twice daily for 29 days. The third group was administered one drop of the combination timolol 0.5% and pilocarpine 2% twice daily for seven days and timolol 0.5% and pilocarpine 4% twice daily for another 22 days. On the 49th day, all of the patients were

measured for IOP immediately before the administration of the morning drop and then every second hour.

The results of this study showed that the mean IOP for a 24 hour period and the diurnal variation were adequately controlled by a single drop combination of timolol and pilocarpine administered twice daily. Both concentrations of the single drop combination of timolol and pilocarpine were more efficacious than timolol alone for controlling IOP and its diurnal variation. Though there was a slight trend in favor of the higher concentration, it was not possible to ascertain whether the single drop combination of timolol 0.5% and pilocarpine 4% was more efficacious than timolol 0.5% and pilocarpine 2%. This could probably be explained by the fact that there was only a small number of patients involved in the study. Simplified administration schedule and the success of this study, though, provides credence to consider the combination drug as an important contributor in managing POAG.

Diagnosing glaucoma and acknowledging the available treatment drugs are only the initial phases. Determining the appropriate regimen suitable for a given patient is the next, vital step. How POAG should be treated and managed is a very controversial issue. Though most doctors concur that medical therapy should be the initial regimen, there is dissagreement as to when other forms of treatment such as lasers and surgery can be considered. Today's standard of care, however, still dictates that medical therapy be first initiated, then laser treatment, and if these two fail; surgical therapy should be introduced.

In the initial stages of attempting therapy through anti-glaucoma medicine, there are several factors the doctor must consider in selecting the appropriate drug to suit the specific needs of the patient. A

patient's systemic and ocular health status are perhaps the most significant factors to acknowledge. For example, a nonselective beta blocker would be contraindicated in a person with respiratory difficulties. Thus, it is highly recommended that a patient receive a thorough physical examination by his/her primary physician before initiating treatment. Similarly, it is also crucial to know what medications the patient is currently taking to prevent unwanted drug interactions. Because glaucoma is more prevalent among older individuals and older individuals are also more likely to have ocular and systemic problems, the significance of these factors become even more amplified.

Cost and compliance are two other factors that the doctor also must consider in selecting the appropriate drug therapy. Glaucoma medications are very expensive. Thus, the doctor must confer with the patient in determining the most economical drug of choice. This will enhance patient compliance as well. Compliance can also be maximized by selecting the simplest treatment possible.

The doctor must also establish a target pressure for the glaucoma patient. The efficacies for the major drugs used in treatment of POAG have previously been stated. How does the doctor establish a target pressure for a particular patient? As a general rule, the greater the damage to the optic nerve head and visual field, the lower the target IOP should be to avoid further visual loss. There are no documented methods currently available to determine for any given optic nerve what pressure should be maintained to prevent the onset or progression of damage. However, the doctor must consider the present IOP as well as the amount of damage that has occurred at that pressure. For

example, if there has been moderate optic nerve damage at a pressure in the 40's, then a pressure reduction to the low 20's may be acceptable. However, if the same amount of damage has occurred to a patient with pressures in the 20's, then a reduction of IOP to the teens may be acceptable.

In attempting to determine the hierarchy of treatment, today's standard of care dictates that initiation of therapy should first be with beta blockers, assuming the patient has no contraindications to the drug. If further reduction in IOP is required, either an adrenergic agent or a miotic is concurrently administered with the beta blockers. While adrenergic agents are often added when only a small drop of IOP is desired, miotics are chosen when larger reductions are required. In addition, if control is still inadequate with a combination of beta blockers and miotics; adrenergics may then be added. Carbonic anhydrase inhibitors can also be added to this drug regimen if success is yet not attained. At this stage, the patient would be considered to be on maximum medical therapy. An example of a typical flow chart to follow in treating POAG is shown in Fig. 1.

A second agent will usually not be fully additive to the first agent. The additive benefit of the two agents will depend to some extent on whether they have a similar mechanism of action. For example, beta blockers and carbonic anhydrase inhibitors can be used effectively together but their effects are only partially additive since both drugs reduce aqueous secretion. On the other hand, beta blockers and miotics are very useful together even though their effects are not fully additive. They represent a good combination since beta blockers reduce aqueous inflow and miotics improve outflow. There is

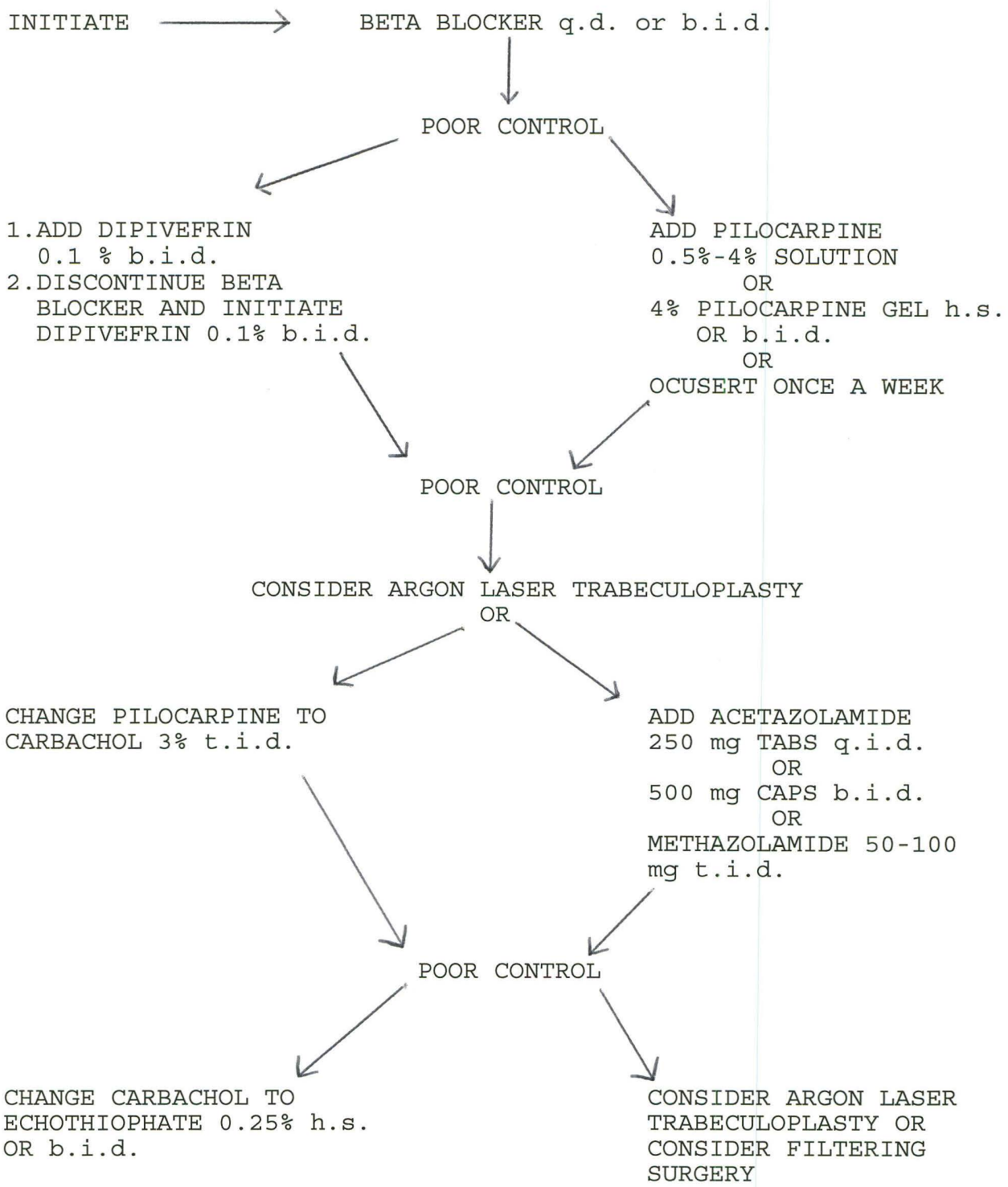

Figure 1. An example of a typical flow chart to follow in maximizing medical therapy of primary open-angle glaucoma

some question as to whether there is a significant added benefit when adding a adrenergic agent to a beta blocker. However, there is recent evidence that suggests that adrenergics used in combination with betaxolol may have a greater additive effect than those seen in combination with nonspecific beta blockers.

Beta blockers will not be the first drug of choice for all patients with POAG. Again, the doctor must keep in mind important factors such as systemic and ocular health conditions. Sometimes adrenergics, especially dipivefrin, are a valuable alternative initial treatment. Miotics are used less often as an initial drug of choice. They have more ocular side effects and require more frequent dosage schedules which can result in poor patient acceptance and reduced compliance. Carbonic anhydrase inhibitors are also seldom chosen as the initial drug of choice because of the associated side effects.

After the first drug of choice has been selected, the next important step is patient education. The patient should be informed about glaucoma and its treatment. The more the patient understands about the disease, the more likely he/she will be to comply with the prescribed regimen. As an example, it is important to explain how the elevated IOP causes damage to the eye as well as how the treatment helps to control this pressure. The doctor should carefully instruct the patient on how to instill the drops and properly use punctal occlusion to reduce the incidence of side effects. Finally, the doctor should also provide the patient written instructions for the drops including when they are to be taken. As a side note, it is often helpful to use the color of the caps as a guide.

The next phase involves testing for the efficacy of the drug in lowering intraocular pressure. It is suggested that a uniocular therapeutic trial be performed in which one eye is treated with the drug, while the other is used as a control. This trial requires either symmetry in IOP or a consistent ratio between the two eyes. It also requires that both eyes have similar diurnal and long-term fluctuations which is usually not the case. It is also important to note that the various categories of drugs will each require different time periods for the evaluation. Miotics can be evaluated within one week after beginning treatment. Adrenergic agents and beta blockers, on the other hand, should be evaluated at least 2 to 4 weeks after initiation of treatment because it takes longer for them to reach their hypotensive effect. As an example of a uniocular trial, a patient's initial IOP's were OD 30 mm Hg and OS 26 mm Hg. Treatment was administered only on the right eye. A two week follow-up showing OD 22 mm Hg and OS 28 mm Hg could reveal that the drug was effective. Such positive results would persuade the doctor to initiate treatment in both eyes.

Once the doctor has prescribed the drug of choice, the next step is determining the frequency of follow-up care and the tests that will be performed at those visits. An important factor in these decisions is the severity of the disease. Regardless of the severity of the glaucoma, IOP should be checked every three months. At these visits, the doctor should carefully question the patient about compliance. Specifically, the doctor must inquire as to the times the medications are taken every day as well as when the last medication was administered. It is also important to determine if the patient is experiencing any ocular or systemic side effects. Blood pressure and pulse should also

be taken at these visits, especially for those on beta blockers. It is suggested to perform dilated fundus exams and threshold visual fields every 6 months or every year depending on the severity of the glaucoma. If the glaucoma is advanced, these tests may be completed every three months. Gonioscopy is usually performed once a year. It is important to keep good patient records at each follow-up visit. An example of a glaucoma summary sheet is shown in Fig. 2.

Another important part of the follow-up visits is evaluating the efficacy of the medication and making any necessary modifications in the drug therapy. Progression of visual field loss, progression of optic nerve damage, and lack of IOP control are three primary factors the doctor examines in considering a change in treatment plan. At times, all three of these factors may be challenging to interpret. Progression of optic disc damage can especially be difficult to assess in myopic patients with physiologically large cups, tilting of the disc, myopic conus, and peripapillary atrophy. In patients with advanced glaucoma, since there has already been extensive damage to the optic nerve it may not be possible to document changes in the thin, atrophic, or absent rim of glial tissue.

There are also many inadequacies in making therapeutic decisions based on the visual fields. Because of short-term and long-term fluctuations innate in visual field testing, this sets limits on the doctor's ability to identify glaucomatous changes. Fluctuations which are usually greater in the areas of glaucomatous fields further adds to the difficulty in determining progression of visual field loss. Uncooperative patients will also decrease the value of visual field testing.

Because of these various reasons, intraocular pressure may at

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DATE	IOP			DF	VF	GN	C/D	MEDS / TX	COMMENTS
	OD	OS	Time						
9/12/91	23	22	9am			x	.5/.5	propine bid ou	repeat vf next visit
12/14/91	18	18	10am	x	x		.5/.5	same	good response to propine

Fig. 2

times be the only meaningful parameter to follow when making therapeutic decisions. Unfortunately, there are also some limitations in using IOP. It is difficult to know if the treatment is adequately controlling the patient's diurnal variation. For practical purposes, pressures are assessed only during office hours. If the patient's high point in their diurnal curve is late at night, the doctor may not know how well this is being controlled. In addition, patients may be reluctant to have office diurnal curves performed on a regular basis due to their own personal time constraints. If this is not possible, an attempt should be made to schedule patients at different times of the day for each subsequent office visit in order to at least obtain a partial profile of their diurnal variation. It is also important to note that intraocular pressure measurements that are taken just before the next administration of the drug provide a better measure of IOP control then pressures that are taken soon after a drug was administered.

When medical therapy fails to achieve a desired objective, the doctor must consider other forms of treatment. The progression of glaucomatous damage or the inability to control IOP are not the only circumstances when the doctor looks for another answer. For example, poor patient compliance and intolerance to medications because of side effects are some situations where treatment such as laser surgery may be a better solution.

Though there are some doctors that advocate the use of lasers as the initial treatment of glaucoma, today's standard of care still dictates that medical therapy be initiated first before other regimens such as lasers are pursued. Laser trabeculoplasty is the most popular laser procedure to lower intraocular pressure. An argon laser is used

to burn scars in the trabecular meshwork. The scars cause the surrounding tissue to contract and open the channels through which the aqueous passes. If laser treatment still does not provide adequate control of IOP and glaucomatous damage, the next mode of therapy is filtration surgery. Trabeculectomy is the most frequently chosen procedure. Because of the risk for major ocular complications, this type of surgery is used as a last resort.

In summary, it has been demonstrated that diagnosis as well as treatment and management of POAG is a significant challenge to the eye care professional. There are various diagnostic tools such as IOP elevations, optic disc changes, and visual field defects available to first indicate the presence of the disease. Once diagnosed, the doctor will generally begin with some form of drug therapy. The eye care provider must choose among the various drugs that best fits the clinical situation. Though beta blockers are the first of choice, they may not effectively treat all glaucomatous cases. Many of the drugs are patient-specific and can cause certain side effects. There are also various steps that the doctor must take in managing the disease. Finally, it was noted that lasers and surgery are used after medical therapy has failed. Unfortunately, there is no simple "formula" in any aspect of diagnosing, treating, or managing glaucoma. The doctor must weigh documented studies with personal experience. Hopefully, continued research will clarify some of the unanswered questions and make POAG less challenging for the doctor in the future.

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